FOR OFFICIAL USE ONLY

160666

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

Examiner # (Mandatory): 72399 Requester's Full Name: Laura L. Stockton

Art Unit 1626 Location (Bldg/Room#): REM 5A01 Phone (circle 305 306 308) 571/272-0710

Serial Number: 10/784,917 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention SEE ATTACHED BIB

Inventors (please provide full names): SEE ATTACHED BIB

Earliest Priority Date: SEE ATTACHED BIB

Keywords (include any known synonyms registry numbers, explanation of initialisms):

409.91
8.00
1-35
4/6.35
4 5 35

RECEIVED
JUL 27 2005
(STIC)

Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

Claims attached - claims 9-11 ~~7-11~~ and B only

elected species (see attached)

Core:

15:13
14:56-16:1

STAFF USE ONLY

Searcher: Mary

Searcher Phone #: _____

Searcher Location: _____

Date Picked Up: 7/19

Date Completed: 7/19

Clerical Prep Time: _____

Terminal Time: 17

Number of Databases: _____

Type of Search

_____ N.A. Sequence
_____ A.A. Sequence
2 Structure (#)
_____ Bibliographic
_____ Litigation1
_____ Fulltext
_____ Procurement
_____ Other

Vendors (include cost where applicable)

4.65.25 STN
_____ Questel/Orbit
_____ Lexis/Nexis
_____ WWW/Internet
_____ In-house sequence systems (list)
_____ Dialog
_____ Dr. Link
_____ Westlaw
_____ Other (specify)

PTO-1590 (2-99)

STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 160666

TO: Laura Stockton **Location: REM/5A01/5C18** **Art Unit: 1626** **Friday, August 19, 2005** **Case Serial Number: 10/784917**	**From: Mary Hale** **Location: Biotech/Chem Library** **Rem 1D86** **Phone: 2-2507** **Mary.Hale@uspto.gov**

Search Notes

Feel free to contact me if you have any questions.

Note -- results are printed on both sides of printout

```
=> dis his

     (FILE 'HOME' ENTERED AT 14:56:18 ON 19 AUG 2005)

     FILE 'REGISTRY' ENTERED AT 14:58:18 ON 19 AUG 2005
L1             STR
L2           0 S L1
L3           1 S L1 FUL

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:00:16 ON 19 AUG 2005
L4           0 FILE MEDLINE
L5           0 FILE BIOSIS
L6           0 FILE EMBASE
L7           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L8           1 S L3

     FILE 'REGISTRY' ENTERED AT 15:01:53 ON 19 AUG 2005
L9             STR L1
L10           50 S L9
L11         5788 S L9 FUL

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:04:10 ON 19 AUG 2005
L12           36 FILE MEDLINE
L13          337 FILE BIOSIS
L14          964 FILE EMBASE
L15          522 FILE CAPLUS
     TOTAL FOR ALL FILES
L16         1859 S L11
L17      2428283 FILE MEDLINE
L18      3250801 FILE BIOSIS
L19      1419137 FILE EMBASE
L20      3099346 FILE CAPLUS
     TOTAL FOR ALL FILES
L21     10197567 S (PHARMAC? OR COMBINATOR? LIBRAR? OR COMPOS?)
L22           28 FILE MEDLINE
L23          236 FILE BIOSIS
L24          804 FILE EMBASE
L25          157 FILE CAPLUS
     TOTAL FOR ALL FILES
L26         1225 S L16 AND L21
L27       186701 FILE MEDLINE
L28       365178 FILE BIOSIS
L29       145295 FILE EMBASE
L30       147528 FILE CAPLUS
     TOTAL FOR ALL FILES
L31       844702 S (TREAT? OR PREVENT? OR THERAP?)(5A)DISEASE?
L32            1 FILE MEDLINE
L33           81 FILE BIOSIS
L34           85 FILE EMBASE
L35           43 FILE CAPLUS
     TOTAL FOR ALL FILES
L36          210 S L26 AND L31
L37          447 FILE MEDLINE
L38          676 FILE BIOSIS
L39          302 FILE EMBASE
L40          943 FILE CAPLUS
     TOTAL FOR ALL FILES
L41         2368 S TANG P?/AU
L42         1354 FILE MEDLINE
```

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

```
L43          1773 FILE BIOSIS
L44          1108 FILE EMBASE
L45          4875 FILE CAPLUS
     TOTAL FOR ALL FILES
L46          9110 S SUN L?/AU
L47           122 FILE MEDLINE
L48           223 FILE BIOSIS
L49           106 FILE EMBASE
L50           220 FILE CAPLUS
     TOTAL FOR ALL FILES
L51           671 S MCMAHON G?/AU
L52            53 FILE MEDLINE
L53            99 FILE BIOSIS
L54            54 FILE EMBASE
L55            65 FILE CAPLUS
     TOTAL FOR ALL FILES
L56           271 S SHAWVER L?/AU
L57             0 FILE MEDLINE
L58             2 FILE BIOSIS
L59             0 FILE EMBASE
L60             3 FILE CAPLUS
     TOTAL FOR ALL FILES
L61             5 S L41 AND L46 AND L51 AND L56
L62             5 DUP REM L61 (0 DUPLICATES REMOVED)
L63             0 FILE MEDLINE
L64             5 FILE BIOSIS
L65             0 FILE EMBASE
L66            10 FILE CAPLUS
     TOTAL FOR ALL FILES
L67            15 S L36 AND (L41 OR L46 OR L51 OR L56)
L68             0 FILE MEDLINE
L69             5 FILE BIOSIS
L70             0 FILE EMBASE
L71             8 FILE CAPLUS
     TOTAL FOR ALL FILES
L72            13 S L67 NOT L61
L73            13 DUP REM L72 (0 DUPLICATES REMOVED)

=> fil reg;d l3 que stat;d ide can
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                409.91     745.42

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                -4.38      -5.11

FILE 'REGISTRY' ENTERED AT 15:09:50 ON 19 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   18 AUG 2005  HIGHEST RN 860995-12-6
DICTIONARY FILE UPDATES:  18 AUG 2005  HIGHEST RN 860995-12-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.


Prepared by: Mary Hale @2-2507 Rem Bldg 1D86
```

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

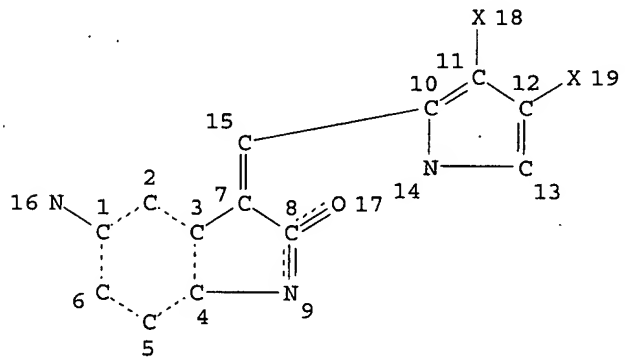
Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

L1 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L3 1 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 5 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.02

YOU HAVE REQUESTED DATA FROM FILE 'BIOSIS, CAPLUS' - CONTINUE? (Y)/N:n

=> fil medl,biosis,embase,caplus;d 18 ibib abs hitstr

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.43	745.85

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-5.11

FILE 'MEDLINE' ENTERED AT 15:10:27 ON 19 AUG 2005

FILE 'BIOSIS' ENTERED AT 15:10:27 ON 19 AUG 2005

FILE 'EMBASE' ENTERED AT 15:10:27 ON 19 AUG 2005

FILE 'CAPLUS' ENTERED AT 15:10:27 ON 19 AUG 2005

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	1998:147306 CAPLUS
DOCUMENT NUMBER:	128:204803
TITLE:	Indolinone combinatorial libraries and related products and methods for the treatment of disease
INVENTOR(S):	Tang, Peng Cho; Sun, Li; McMahon, Gerald; Hirth, Klaus Peter; Shawver, Laura Kay; et al.
PATENT ASSIGNEE(S):	Sugen, Inc., USA; Tang, Peng Cho; Sun, Li; McMahon, Gerald
SOURCE:	PCT Int. Appl., 293 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	12

PATENT INFORMATION:

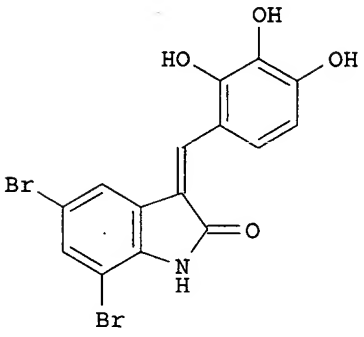
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807695	A1	19980226	WO 1997-US14736	19970820
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CN 1155838	A	19970730	CN 1996-190616	19960605
CA 2264220	AA	19980226	CA 1997-2264220	19970820
EP 929520	A1	19990721	EP 1997-939480	19970820
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001503736	T2	20010321	JP 1998-510973	19970820
EP 1247803	A2	20021009	EP 2002-77564	19970820
EP 1247803	A3	20021016		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

AU 9741556	A1	19980306	AU 1997-41556		19970821
PRIORITY APPLN. INFO.:			US 1996-702232	A	19960823
			US 1996-31585P	P	19961205
			US 1996-31586P	P	19961205
			US 1996-31588P	P	19961205
			US 1996-32546P	P	19961205
			US 1996-32547P	P	19961205
			US 1997-45565P	P	19970505
			US 1997-45566P	P	19970505
			US 1997-45714P	P	19970505
			US 1997-45715P	P	19970505
			US 1997-46843P	P	19970505
			EP 1997-939480	A3	19970820
			WO 1997-US14736	W	19970820

OTHER SOURCE(S): MARPAT 128:204803

GI



I

AB The invention relates to indolinone derivs. capable of modulating, regulating, and/or inhibiting protein kinase signal transduction. The compds. are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis, and restenosis, and metabolic diseases such as diabetes. Inhibitors specific to the FLK protein kinase can be obtained by adding chemical substituents to the 3-[(indole-3-yl)methylene]-2-indolinone system, in particular at the 1' position of the indole ring. Indolinone compds. that specifically inhibit the FLK and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano[b]pyrrole moiety. Indolinone compds. that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosol. indolinone compds. that are tyrosine kinase inhibitors, and related products and methods. Approx. 1200 title compds., such as I, were prepared by combinatorial condensation of certain (un)substituted indolinones with aldehydes at the 3-position. I gave complete inhibition of MET kinase at chimeric MET receptors in vitro.

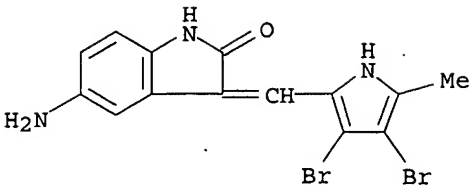
IT **204004-29-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation and testing of indolinone combinatorial library as protein kinase inhibitors)

RN 204004-29-5 CAPLUS

CN 2H-Indol-2-one, 5-amino-3-[(3,4-dibromo-5-methyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> fil reg;d l11 que stat

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.94	753.79

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.73	-5.84

FILE 'REGISTRY' ENTERED AT 15:11:00 ON 19 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 18 AUG 2005 HIGHEST RN 860995-12-6
DICTIONARY FILE UPDATES: 18 AUG 2005 HIGHEST RN 860995-12-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

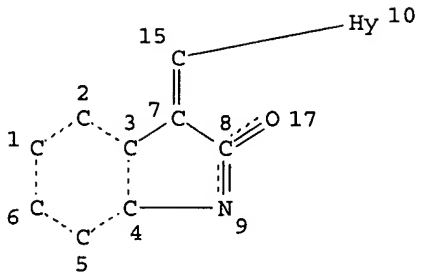
```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************
```

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

L9 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
L11 5788 SEA FILE=REGISTRY SSS FUL L9

100.0% PROCESSED 26325 ITERATIONS 5788 ANSWERS
SEARCH TIME: 00.00.01

=> dis his l11-

(FILE 'REGISTRY' ENTERED AT 15:01:53 ON 19 AUG 2005)
L11 5788 S L9 FUL

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:04:10 ON 19 AUG 2005
L12 36 FILE MEDLINE
L13 337 FILE BIOSIS
L14 964 FILE EMBASE
L15 522 FILE CAPLUS
TOTAL FOR ALL FILES
L16 1859 S L11
L17 2428283 FILE MEDLINE
L18 3250801 FILE BIOSIS
L19 1419137 FILE EMBASE
L20 3099346 FILE CAPLUS
TOTAL FOR ALL FILES
L21 10197567 S (PHARMAC? OR COMBINATOR? LIBRAR? OR COMPOS?)
L22 28 FILE MEDLINE
L23 236 FILE BIOSIS
L24 804 FILE EMBASE
L25 157 FILE CAPLUS
TOTAL FOR ALL FILES
L26 1225 S L16 AND L21
L27 186701 FILE MEDLINE
L28 365178 FILE BIOSIS
L29 145295 FILE EMBASE
L30 147528 FILE CAPLUS
TOTAL FOR ALL FILES
L31 844702 S (TREAT? OR PREVENT? OR THERAP?)(5A)DISEASE?
L32 1 FILE MEDLINE

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

```
L33           81 FILE BIOSIS
L34           85 FILE EMBASE
L35           43 FILE CAPLUS
     TOTAL FOR ALL FILES
L36          210 S L26 AND L31
L37          447 FILE MEDLINE
L38          676 FILE BIOSIS
L39          302 FILE EMBASE
L40          943 FILE CAPLUS
     TOTAL FOR ALL FILES
L41         2368 S TANG P?/AU
L42         1354 FILE MEDLINE
L43         1773 FILE BIOSIS
L44         1108 FILE EMBASE
L45         4875 FILE CAPLUS
     TOTAL FOR ALL FILES
L46         9110 S SUN L?/AU
L47          122 FILE MEDLINE
L48          223 FILE BIOSIS
L49          106 FILE EMBASE
L50          220 FILE CAPLUS
     TOTAL FOR ALL FILES
L51          671 S MCMAHON G?/AU
L52           53 FILE MEDLINE
L53           99 FILE BIOSIS
L54           54 FILE EMBASE
L55           65 FILE CAPLUS
     TOTAL FOR ALL FILES
L56          271 S SHAWVER L?/AU
L57            0 FILE MEDLINE
L58            2 FILE BIOSIS
L59            0 FILE EMBASE
L60            3 FILE CAPLUS
     TOTAL FOR ALL FILES
L61            5 S L41 AND L46 AND L51 AND L56
L62            5 DUP REM L61 (0 DUPLICATES REMOVED)
L63            0 FILE MEDLINE
L64            5 FILE BIOSIS
L65            0 FILE EMBASE
L66           10 FILE CAPLUS
     TOTAL FOR ALL FILES
L67           15 S L36 AND (L41 OR L46 OR L51 OR L56)
L68            0 FILE MEDLINE
L69            5 FILE BIOSIS
L70            0 FILE EMBASE
L71            8 FILE CAPLUS
     TOTAL FOR ALL FILES
L72           13 S L67 NOT L61
L73           13 DUP REM L72 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 15:09:50 ON 19 AUG 2005

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:10:27 ON 19 AUG 2005

     FILE 'REGISTRY' ENTERED AT 15:11:00 ON 19 AUG 2005

=> fil medl,biosis,embase,caplus;d l62 1-5 ibib abs hitstr;dis his l63-;d 1-13 l73
ibib abs
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
```

FULL ESTIMATED COST	1.29	755.08
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-5.84

FILE 'MEDLINE' ENTERED AT 15:12:46 ON 19 AUG 2005

FILE 'BIOSIS' ENTERED AT 15:12:46 ON 19 AUG 2005

FILE 'EMBASE' ENTERED AT 15:12:46 ON 19 AUG 2005

FILE 'CAPLUS' ENTERED AT 15:12:46 ON 19 AUG 2005

L62 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:168826 BIOSIS
DOCUMENT NUMBER: PREV200400170685
TITLE: 3-(piperazinylbenzylidenyl)-2-indolinone compounds and derivatives as protein tyrosine kinase inhibitors.
AUTHOR(S): **Tang, Peng Cho** [Inventor, Reprint Author]; **Sun, Li** [Inventor]; **McMahon, Gerald** [Inventor]; **Shawver, Laura Kay** [Inventor]; Hirth, Klaus Peter [Inventor]
CORPORATE SOURCE: Forest City, CA, USA
ASSIGNEE: Sugen, Inc.
PATENT INFORMATION: US 6696448 20040224
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Feb 24 2004) Vol. 1279, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2004
Last Updated on STN: 24 Mar 2004
AB The present invention relates to novel 3-(piperazinyl-benylidenyl)-2-indolinone compounds and derivatives and physiologically acceptable salts thereof which are expected to modulate the activity of protein tyrosine kinases and therefore to be useful in the prevention and treatment of protein tyrosine kinase related cellular disorders such as cancer.

L62 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:262328 BIOSIS
DOCUMENT NUMBER: PREV200100262328
TITLE: Indolinone combinatorial libraries and related products and methods for the treatment of disease.
AUTHOR(S): **Tang, Peng Cho** [Inventor]; **Sun, Li** [Inventor]; **McMahon, Gerald** [Inventor]; Hirth, Klaus Peter [Inventor]; **Shawver, Laura Kay** [Inventor, Reprint author]
CORPORATE SOURCE: San Francisco, CA, USA
ASSIGNEE: Sugen, Inc.
PATENT INFORMATION: US 6147106 20001114
SOURCE: Official Gazette of the United States Patent and Trademark

Office Patents, (Nov. 14, 2000) Vol. 1240, No. 2. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 30 May 2001
Last Updated on STN: 19 Feb 2002

AB The present invention relates to organic molecules capable of modulating, regulating and/or inhibiting protein kinase signal transduction. Such compounds are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis and restenosis and metabolic diseases such as diabetes. The present invention features indolinone compounds that potently inhibit protein kinases and related products and methods. Inhibitors specific to the FLK protein kinase can be obtained by adding chemical substituents to the 3-[(indole-3-yl)methylene]-2-indolinone, in particular at the 1' position of the indole ring. Indolinone compounds that specifically inhibit the FLK and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano-b-pyrrol moiety. Indolinone compounds that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosoluble indolinone compounds that are tyrosine kinase inhibitors and related products and methods.

L62 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:626172 CAPLUS
DOCUMENT NUMBER: 131:257441
TITLE: Heterocyclic families of compounds [tricyclic-based indolinones and pyrazolecarboxylic acid amides] for the modulation of tyrosine protein kinase
INVENTOR(S): Fong, Annie; Hannah, Alison; Harris, David G.; Hirth, Peter; Hubbard, Steven R.; Langecker, Peter; Liang, Congxin; **McMahon, Gerald**; Mohammadi, Moosa; Schlessinger, Joseph; **Shawver, Laura K.**; **Sun, Li**; **Tang, Peng C.**; Ullrich, Axel
PATENT ASSIGNEE(S): Sugen, Inc., USA; New York University; Max-Planck Institut fur Biochemie
SOURCE: PCT Int. Appl., 269 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948868	A2	19990930	WO 1999-US6468	19990326
WO 9948868	A3	20000224		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2325935	AA	19990930	CA 1999-2325935	19990326
AU 9933635	A1	19991018	AU 1999-33635	19990326
EP 1066257	A2	20010110	EP 1999-915018	19990326

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2002507598	T2	20020312	JP 2000-537851		19990326
US 6514981	B1	20030204	US 1999-283657		19990401
US 2003203901	A1	20031030	US 2002-302932		20021125
PRIORITY APPLN. INFO.:			US 1998-79713P	P	19980326
			US 1998-80422P	P	19980402
			US 1998-81792P	P	19980415
			US 1998-82056P	P	19980416
			US 1998-89397P	P	19980615
			US 1998-89521P	P	19980616
			US 1998-98783P	P	19980901
			WO 1999-US6468	W	19990326
			US 1999-283657	A3	19990401

OTHER SOURCE(S): MARPAT 131:257441
GI

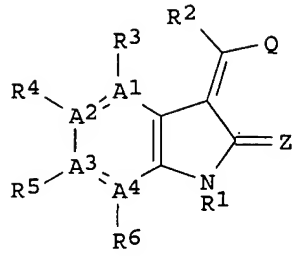
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to certain indolinone-based and pyrazolylamide-based compds., I and II, their method of synthesis, and combinatorial libraries consisting of the compds. [wherein AB = atoms to make up 1-2 fused and/or connected rings; R = aromatic or heteroarom. ring which may form an addnl. ring by cyclization to the methylene group; R1, R2 = H, alkyl, (hetero)aryl or -aliphatic ring, amino, NO2, halo, etc.; R3 = (un)substituted Ph; Z = (un)substituted (CH2)0-3; R4, R5 = H, alkyl, (hetero)aryl or -aliphatic, amine, ketone, etc.]. The invention also relates to methods of modulating the function of protein kinases using these compds., and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways. Data for prepns. and/or biol. activity are given, as well as the prepns. of various oxindole intermediates. For instance, the pyrazolecarboxamide derivative III gave up to 70% inhibition of growth of Calu-6 human lung carcinoma cells as a xenograft in mice. As another example, the indolinone derivative IV was prepared by condensation of 6-(4-methoxyphenyl)-2-oxindole with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde in the presence of piperidine. Extensive tests of a few selected compds. against a variety of protein kinases are described.

L62 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:747592 CAPLUS
DOCUMENT NUMBER: 130:3771
TITLE: Preparation of 3-(hetero)arylmethylidene-2-indolinone derivatives as modulators of protein kinase activity for use in treating cancer.
INVENTOR(S): **Tang, Peng Cho; Sun, Li; McMahon, Gerald; Shawver, Laura Kay;** Hirth, Klaus Peter
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 269 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9850356		A1	19981112	WO 1998-US9017	19980507
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2289102		AA	19981112	CA 1998-2289102	19980507
AU 9876842		A1	19981127	AU 1998-76842	19980507
EP 984930		A1	20000315	EP 1998-924746	19980507
EP 984930		B1	20050406		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002511852		T2	20020416	JP 1998-548319	19980507
AT 292623		E	20050415	AT 1998-924746	19980507
US 6051593		A	20000418	US 1998-99721	19980619
US 6313158		B1	20011106	US 1998-100854	19980619
US 6133305		A	20001017	US 1998-161046	19980925
US 2001056094		A1	20011227	US 2000-482198	20000112
US 2001007033		A1	20010705	US 2000-516948	20000301
US 2002026053		A1	20020228	US 2001-916331	20010730
US 6506763		B2	20030114		
US 2002058661		A1	20020516	US 2001-948106	20010907
US 6696463		B2	20040224		
US 2002183370		A1	20021205	US 2001-29946	20011231
US 6579897		B2	20030617		
US 2004106630		A1	20040603	US 2003-725079	20031202
US 2004106618		A1	20040603	US 2003-725267	20031202
PRIORITY APPLN. INFO.:				US 1997-45838P	P 19970507
				US 1997-46868P	P 19970508
				US 1997-49324P	P 19970611
				US 1997-50412P	P 19970620
				US 1997-50413P	P 19970620
				US 1997-50977P	P 19970620
				US 1997-59336P	P 19970919
				US 1997-59381P	P 19970919
				US 1997-59384P	P 19970919
				US 1997-59544P	P 19970919
				US 1997-59677P	P 19970919
				US 1997-59971P	P 19970925
				US 1997-60194P	P 19970926
				US 1998-74621	A3 19980507
				WO 1998-US9017	W 19980507
				US 1998-100854	A3 19980619
				US 1998-99721	A1 19980619
				US 1998-161046	A3 19980925
				US 2000-482198	A3 20000112
				US 2000-516948	B1 20000301
				US 2001-819698	A3 20010329
OTHER SOURCE(S):		MARPAT 130:3771			
GI					



I

AB Title compds. [I; A1-A4 = C, N; when any of A1-A4 = N, then the corresponding R3-R6 = null; R1 = H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclyl, trihalomethylcarbonyl, OH, CO2H, trihalomethylsulfonyl, etc.; R2 = H, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclyl, halo; R3-R6 = H, alkyl, trihalomethyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclyl, OH, SH, alkoxy, aryloxy, amino, phosphonyl, guanidinyl, NO2, halo, (iso)cyanato, etc.; R3R4 or R4R5 or R5R6 = cycloalkyl, aryl, heteroaryl, heteroalicyclyl, OCH2O, OCH2CH2O; Q = specified (substituted) (hetero)aryl; Z = O, S], were prepared Thus, 3-(4-imidazolylmethylidenyl)-4,6-dimethyl-2-indolinone inhibited CDK2 with IC50 = <0.78 μM.

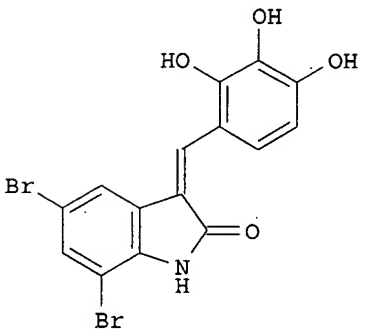
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L62 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:147306 CAPLUS
DOCUMENT NUMBER: 128:204803
TITLE: Indolinone combinatorial libraries and related products and methods for the treatment of disease
INVENTOR(S): **Tang, Peng Cho; Sun, Li; McMahon, Gerald**; Hirth, Klaus Peter; **Shawver, Laura Kay**; et al.
PATENT ASSIGNEE(S): Sugen, Inc., USA; Tang, Peng Cho; Sun, Li; McMahon, Gerald
SOURCE: PCT Int. Appl., 293 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807695	A1	19980226	WO 1997-US14736	19970820
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CN 1155838	A	19970730	CN 1996-190616	19960605
CA 2264220	AA	19980226	CA 1997-2264220	19970820
EP 929520	A1	19990721	EP 1997-939480	19970820
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

	IE, FI				
JP 2001503736	T2	20010321	JP 1998-510973		19970820
EP 1247803	A2	20021009	EP 2002-77564		19970820
EP 1247803	A3	20021016			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
AU 9741556	A1	19980306	AU 1997-41556		19970821
PRIORITY APPLN. INFO.:			US 1996-702232	A	19960823
			US 1996-31585P	P	19961205
			US 1996-31586P	P	19961205
			US 1996-31588P	P	19961205
			US 1996-32546P	P	19961205
			US 1996-32547P	P	19961205
			US 1997-45565P	P	19970505
			US 1997-45566P	P	19970505
			US 1997-45714P	P	19970505
			US 1997-45715P	P	19970505
			US 1997-46843P	P	19970505
			EP 1997-939480	A3	19970820
			WO 1997-US14736	W	19970820

OTHER SOURCE(S): MARPAT 128:204803
GI



I

AB The invention relates to indolinone derivs. capable of modulating, regulating, and/or inhibiting protein kinase signal transduction. The compds. are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis, and restenosis, and metabolic diseases such as diabetes. Inhibitors specific to the FLK protein kinase can be obtained by adding chemical substituents to the 3-[(indole-3-yl)methylene]-2-indolinone system, in particular at the 1' position of the indole ring. Indolinone compds. that specifically inhibit the FLK and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano[b]pyrrole moiety. Indolinone compds. that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosol. indolinone compds. that are tyrosine kinase inhibitors, and related products and methods. Approx. 1200 title compds., such as I, were prepared by combinatorial condensation of certain (un)substituted indolinones with aldehydes at the 3-position. I gave complete inhibition of MET kinase at chimeric MET receptors in vitro.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:04:10 ON 19 AUG 2005)

L63 0 FILE MEDLINE
L64 5 FILE BIOSIS
L65 0 FILE EMBASE
L66 10 FILE CAPLUS
TOTAL FOR ALL FILES
L67 15 S L36 AND (L41 OR L46 OR L51 OR L56)
L68 0 FILE MEDLINE
L69 5 FILE BIOSIS
L70 0 FILE EMBASE
L71 8 FILE CAPLUS
TOTAL FOR ALL FILES
L72 13 S L67 NOT L61
L73 13 DUP REM L72 (0 DUPLICATES REMOVED)

FILE 'REGISTRY' ENTERED AT 15:09:50 ON 19 AUG 2005

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:10:27 ON 19 AUG 2005

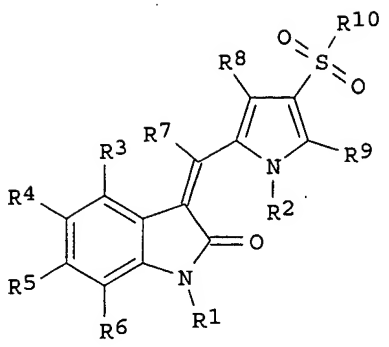
FILE 'REGISTRY' ENTERED AT 15:11:00 ON 19 AUG 2005

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:12:46 ON 19 AUG 2005

L73 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:122809 CAPLUS
DOCUMENT NUMBER: 142:197875
TITLE: Preparation of 3-(5-sulfonylated pyrrol-2-ylmethylene)-2-indolinone derivatives as kinase inhibitors
INVENTOR(S): **Tang, Peng Cho**; Wei, Chung Chen; Xia, Yi
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 67 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005032871	A1	20050210	US 2003-653470		20030903
PRIORITY APPLN. INFO.:			US 2002-407350P	P	20020903

OTHER SOURCE(S): MARPAT 142:197875
GI



I

AB The title compds. (I) or prodrugs or **pharmaceutically** acceptable salts thereof [wherein R1, R2 = H, alkyl, cycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, CO2R11, CONR11R12, C(:S)NR11R12, COR11, S(:O)2R11, SO2NR11R12, P(:O)(OR11)(OR12); R3, R4, R5, R6, R8, R9 = H, halogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicylic, OH, OR11, SH, SR11, NR11R12, -S(:O)2R11, SO2NR11R12, (CH2)nCO2R11, (CH2)nCONR11R12, C(:S)NR11R12, COR11, NR11COR12, -NHCO2R12, -OCO2R11, -OCONR11R12, cyano, NO2, wherein said aryl, heteroaryl and heteroalicyclic groups may be further substituted with alkyl or halogen; wherein n -3; R7 = H, alkyl, cycloalkyl, aryl, heteroaryl, OH, cyano, OR11, -CO2OR11, CONR11R12; R10 = alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, NR11R12, OR11, wherein said aryl group may be substituted with a substituent selected from the group consisting of -C(O)OR11, alkyl or halo; R11, R12 = H, alkyl, cycloalkyl, aryl, heteroaryl or heteroalicyclic, wherein said alkyl or aryl group may be substituted with one or more substituents selected from the group consisting of alkyl, aryl, hydroxy, amino, alkoxy, heteroalicyclic, carbonyl, carboxylic acid and carboxylic ester; alternatively, NR11R12 = (un)substituted 5-7 membered heteroalicyclic or 5-6 membered heteroaryl ring] are prepared These compds. modulate protein kinase activity and are useful in treating disorders related to abnormal kinase activity, in particular various cancers such as pancreatic cancer, breast cancer, lung cancer, laryngeal cancer, ovarian cancer, uterine cancer, skin cancer, prostate cancer, kidney cancer, colon cancer and testicular cancer. **Pharmaceutical compns.** comprising these compds., methods of **treating diseases** utilizing **pharmaceutical compns.** comprising these compds. and methods of preparing them are also disclosed. Thus, a mixture of oxindole, 3-[[4-[2-(dimethylcarbamoyl)ethyl]-5-formyl-2-methyl-1H-pyrrol-3-yl]sulfonyl]benzoic acid (1 equiv) and piperidine (excess) in ethanol (0.2 M) was stirred at between room temperature to 100°. After completion, the mixture was concentrated and then triturated with dilute HCl solution to give 3-[[4-[2-(dimethylcarbamoyl)ethyl]-2-methyl-5-[((3Z)-2-oxo-1,2-dihydroindol-3-ylidene)methyl]-1H-pyrrol-3-yl]sulfonyl]benzoic acid.

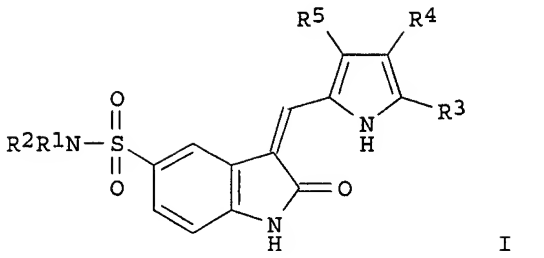
L73 ANSWER 2 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:243075 BIOSIS
DOCUMENT NUMBER: PREV200510030554
TITLE: Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis.
AUTHOR(S): Abdollahi, Amir; Li, Minglun; Ping, Gong; Plathow, Christian; Domhan, Sophie; Kiessling, Fabian; Lee, Leslie B.; **McMahon, Gerald**; Groene, Hermann-Josef;

Lipson, Kenneth E.; Huber, Peter E. [Reprint Author]
CORPORATE SOURCE: German Canc Res Ctr, Dept Radiat Oncol, D-69120 Heidelberg, Germany
p.huber@dkfz.de
SOURCE: Journal of Experimental Medicine, (MAR 21 05) Vol. 201, No. 6, pp. 925-935.
CODEN: JEMEAV. ISSN: 0022-1007.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Jun 2005
Last Updated on STN: 29 Jun 2005
AB Pulmonary fibrosis is the consequence of a variety of **diseases** with no satisfying **treatment** option. Therapy-induced fibrosis also limits the efficacy of chemotherapy and radiotherapy in numerous cancers. Here, we studied the potential of platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitors (RTKIs) to attenuate radiation-induced pulmonary fibrosis. Thoraces of C57BL/6 mice were irradiated (20 Gy), and mice were treated with three distinct PDGF RTKIs (SU9518, SU11657, or Imatinib). Irradiation was found to induce severe lung fibrosis resulting in dramatically reduced mouse survival. Treatment with PDGF RTKIs markedly attenuated the development of pulmonary fibrosis in excellent correlation with clinical, histological, and computed tomography results. Importantly, RTKIs also prolonged the life span of irradiated mice. We found that radiation up-regulated expression of PDGF (A-D) isoforms leading to phosphorylation of PDGF receptor, which was strongly inhibited by RTKIs. Our findings suggest a pivotal role of PDGF signaling in the pathogenesis of pulmonary fibrosis and indicate that inhibition of fibrogenesis, rather than inflammation, is critical to antifibrotic treatment. This study points the way to a potential new approach for treating idiopathic or therapy-related forms of lung fibrosis.

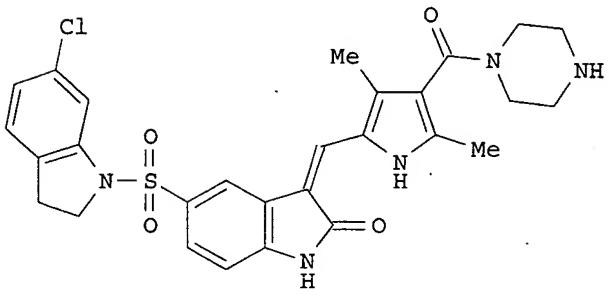
L73 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:857170 CAPLUS
DOCUMENT NUMBER: 141:350032
TITLE: Preparation of 5-sulfonamido-substituted indolinone compounds as protein kinase inhibitors
INVENTOR(S): **Tang, Peng Cho**; Liang, Congxin; Miller, Todd; Lipson, Kenneth E.
PATENT ASSIGNEE(S): Sugen Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 58 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004204407	A1	20041014	US 2004-793952		20040308
PRIORITY APPLN. INFO.:			US 2003-452552P	P	20030307

OTHER SOURCE(S): MARPAT 141:350032
GI



I



II

AB The title compds. [I; R1 and R2 combine to form (un)substituted optionally fused heterocyclic ring; R3-R5 = H, alkyl, hydroxyalkyl, etc.; or R3 and R4 may combine to form a cyclic 6-membered alicyclic ring which may be substituted with one or more lower alkyl] that modulate the activity of protein kinases ("PKs") and are therefore useful in treating disorders related to abnormal PK activity (no biol. data), were prepared General method of synthesis of the compds. I by condensation of oxindoles and aldehydes (preparation of intermediates is given) is described. Eighty-two compds. I (e.g., II) were prepared **Pharmaceutical compns** . comprising the compds. I, methods of **treating diseases** utilizing **pharmaceutical compns.** comprising these compds. and methods of preparing them are also disclosed.

L73 ANSWER 4 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:379167 BIOSIS
DOCUMENT NUMBER: PREV200300379167
TITLE: SU11248 maintenance therapy prevents tumor regrowth after fractionated irradiation of murine tumor models.
AUTHOR(S): Schueneman, Aaron J.; Himmelfarb, Eric; Geng, Ling; Tan, Jiahua; Donnelly, Edwin; Mendel, Dirk; **McMahon, Gerald**; Hallahan, Dennis E. [Reprint Author]
CORPORATE SOURCE: Department of Radiation Oncology, Vanderbilt University, 1301 22nd Avenue South, B-902 The Vanderbilt Clinic, Nashville, TN, 37232-5671, USA
Dennis.Hallahan@mcmail.vanderbilt.edu
SOURCE: Cancer Research, (July 15 2003) Vol. 63, No. 14, pp. 4009-4016. print.
ISSN: 0008-5472 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Aug 2003
Last Updated on STN: 20 Aug 2003
AB Receptor tyrosine kinase activation contributes to cell viability during

cytotoxic therapy. The novel broad spectrum receptor tyrosine kinase inhibitor, SU11248, inhibits vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor, c-kit, and fetal liver tyrosine kinase 3. In this study, we maintained SU11248 plasma levels beyond the completion of radiotherapy to determine whether tumor regrowth can be delayed. The antiangiogenic effects of SU11248 were demonstrated using human umbilical vein endothelial cells in vitro. Apoptosis increased and clonogenic survival decreased when SU11248 was used in combination with radiation from 0 to 6 Gy on endothelial cells. In vivo tumor growth delay was increased in C57B6J mice with Lewis lung carcinoma or glioblastoma multiform (GL261) hind limb tumors. Mice were treated with daily i.p. injections (40 mg/kg) of SU11248 during 7 days of radiation treatment (21 Gy). Combined treatment with SU11248 and radiation significantly reduced tumor volume as compared with either treatment alone. Concomitant reduction in vasculature was confirmed using the dorsal vascular window model. The vascular length established using images taken from a consistent quadrant in the window show the combination therapy was more effective in destroying tumor vasculature than either treatment alone. SU11248 maintenance administration beyond the completion of radiotherapy results in prolongation of tumor control. In summary, SU11248 enhances radiation-induced endothelial cytotoxicity, resulting in tumor vascular destruction and tumor control when combined with fractionated radiotherapy in murine tumor models. Moreover, inhibition of angiogenesis well beyond radiation therapy may be a promising treatment paradigm for refractory human neoplasms.

L73 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:927188 CAPLUS
DOCUMENT NUMBER: 138:14005
TITLE: Preparation of 5-aralkylsulfonyl-3-(pyrrol-2-ylmethylidene)-2-indolinone derivatives as kinase inhibitors
INVENTOR(S): Cui, Jingrong; Ramphal, Yudhi; Liang, Congxin; **Sun, Li**; Wei, Chung Chen; **Tang, Peng Cho**
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 479 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002096361	A2	20021205	WO 2002-US16841	20020530
WO 2002096361	A3	20030313		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003125370	A1	20030703	US 2002-157007	20020530
US 6599902	B2	20030729		

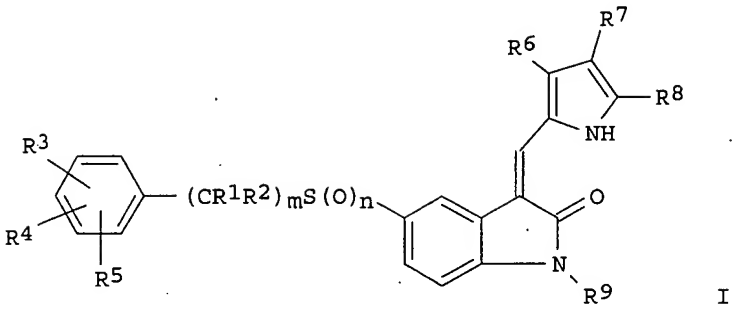
PRIORITY APPLN. INFO.: US 2001-294544P P 20010530

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

US 2001-328408P P 20011010

OTHER SOURCE(S): MARPAT 138:14005

GI



I

AB The present invention relates to certain 5-aralkylsulfonyl-3-(pyrrol-2-ylmethylidene)-2-indolinone derivs. (shown as I; see below for variable definitions; e.g. 2,4-dimethyl-5-(2-oxo-5-phenylmethanesulfonyl-1,2-dihydroindol-(3Z)-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide) that inhibit kinases (no data), in particular met kinase. **Pharmaceutical compns.** comprising these compds., methods of **treating diseases** mediated by kinases using **pharmaceutical compns.** comprising these compds., and methods of preparing them are also disclosed. In I: n = 0-2; m = 1-3; R1 and R2 = H or alkyl; R3, R4, and R5 = H, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, alkoxycarbonyl, haloalkoxy, cyano, carboxy, carboxyalkyl, nitro, aryl, aryloxy, heteroaryl, heteroaryloxy, -(alkylene)-CONR10R11, -CONR10R11, or - NR10R11 (R10 is H or alkyl, and R11 is aryl, heteroaryl, heterocycle, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, acetylalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, heteroaralkyl, aralkyl, or heterocyclylalkyl wherein the alkyl chain in aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl is optionally substituted with one or two hydroxy, or R10 and R11 together with the N atom to which they are attached combine to form saturated or unsatd. heterocycloamino). R6 is H, alkyl, cycloalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, heterocyclylalkyl, aryl, heteroaryl, carboxy, alkoxycarbonyl, heterocyclylcarbonyl, aminoalkylcarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, -CONR10R11 or -(alkylene)-CONR10R11. R7 and R8 = H, alkyl, cycloalkyl, heterocyclylalkyl, -COR12, -(alkylene)-COR12 (R12 = alkoxy, hydroxy, or heterocycle, alkylamino, dialkylamino), -SO2R14, -CONR13R14, or -(alkylene)-CONR13R14 (R13 is H or alkyl, and R14 is aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, acetylalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, heteroaralkyl, or heterocyclylalkyl wherein the alkyl chain in aminoalkyl, heteroaralkyl, heteroaralkyl, or heterocyclylalkyl is optionally substituted with one or two hydroxy group(s), or when R13 and R14 are attached to a N atom R13 and R14 together with the N atom to which they are attached form saturated or unsatd. heterocycloamino). R6 and R7 or R7 and R8 can combine to form a saturated or unsatd. 5 to 8 membered ring; and R9 is: H or alkyl; -PO(OR15)2 where each R15 = H or alkyl; -COR16 where R16 is H or alkyl; or -CHR17NR18R19 where R17 is H or alkyl, and R18 and R19 = H or alkyl or R18 and R19 together with the N atom to which they are attached form heterocycloamino. Although the methods of preparation are not claimed, 375 example prepns. of I

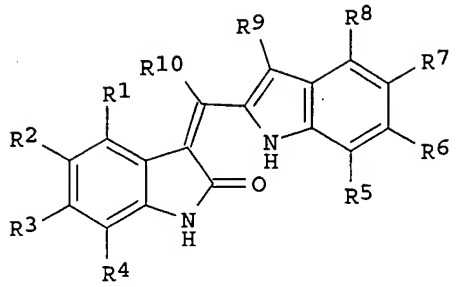
plus addnl. prepns. of intermediates are included.

L73 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:904107 CAPLUS
DOCUMENT NUMBER: 136:37505
TITLE: Preparation of 3-(2-indolylmethylene)-2-indolinones as protein kinase/phosphatase inhibitors for **treatment** of proliferative **diseases**
INVENTOR(S): **Tang, Peng Cho**; Harris, G. Davis; Li, Xiaoyuan
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 199 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

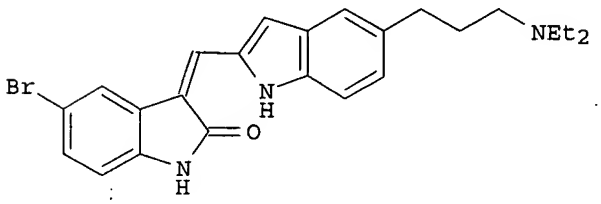
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001094312	A2	20011213	WO 2001-US17961	20010604
WO 2001094312	A3	20020808		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2410509	AA	20011213	CA 2001-2410509	20010604
US 2002052369	A1	20020502	US 2001-871700	20010604
US 6706709	B2	20040316		
EP 1294688	A2	20030326	EP 2001-946059	20010604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003535847	T2	20031202	JP 2002-501862	20010604
US 2004147586	A1	20040729	US 2003-725277	20031202

PRIORITY APPLN. INFO.:		
US 2000-209162P	P	20000602
US 2001-871700	A3	20010604
WO 2001-US17961	W	20010604

OTHER SOURCE(S): MARPAT 136:37505
GI



I



II

AB Title compds. I [wherein R4-R6 and R8-R10 = H; R1, R2, and R3 = independently H, halo, carboxylic acid, trihalomethyl, or (un)substituted ester, amide, alkyl, alkoxy, or (hetero)aryl; R7 = (un)substituted alkyl or alkoxy; or **pharmaceutically** acceptable salt thereof] were prepared as modulators of the activity of protein kinases (PKs) and phosphatases. For example, 5-bromo-2-oxindole was coupled with 5-(3-diethylaminopropyl)-1H-indole-2-carbaldehyde (preparation given) in the presence of piperidine in EtOH to afford II, which inhibited GST-FLK-1, EGF receptor kinase, and PDGF with IC50 values of 0.03 μM, 2.87 μM, and 0.38 μM, resp. I are useful in treating disorders related to abnormal PK activity, such as blood vessel proliferative disorders, mesangial cell proliferative disorders, fibrotic disorders, cancer, diabetes, autoimmune disorders, hyperproliferation disorders, restenosis, fibrosis, psoriasis, von Heppel-Lindau disease, osteoarthritis, rheumatoid arthritis, angiogenesis, inflammatory disorders, immunol. disorders, and cardiovascular disorders (no data). **Combinatorial libraries** comprising at least five indolinone compds., formed by reacting oxindoles with aldehydes, are also claimed.

L73 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:868415 CAPLUS
DOCUMENT NUMBER: 136:697
TITLE: Mannich base prodrugs of 3-(pyrrol-2-ylmethylidene)-2-indolinone derivatives
INVENTOR(S): Moon, Malcolm Wilson; Morozowich, Walter; Gao, Ping; **Tang, Peng Cho**
PATENT ASSIGNEE(S): Sugen, Inc., USA; Pharmacia & Upjohn Company
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001090068	A2	20011129	WO 2001-US16757		20010524
WO 2001090068	A3	20020606			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2408709	AA	20011129	CA 2001-2408709		20010524
AU 2001064885	A5	20011203	AU 2001-64885		20010524
US 2002032204	A1	20020314	US 2001-863804		20010524
US 6710067	B2	20040323			
US 2002035140	A1	20020321	US 2001-863905		20010524
US 6451838	B2	20020917			
US 2002037878	A1	20020328	US 2001-863819		20010524
US 6482848	B2	20021119			
EP 1301507	A2	20030416	EP 2001-939357		20010524
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003534323	T2	20031118	JP 2001-586257		20010524
US 2003045565	A1	20030306	US 2002-243663		20020916
US 2003083363	A1	20030501	US 2002-243942		20020916
US 6716870	B2	20040406			
US 2004127542	A1	20040701	US 2003-429895		20030505
US 2004127544	A1	20040701	US 2003-743909		20031224
US 2005107340	A1	20050519	US 2004-774415		20040210
PRIORITY APPLN. INFO.:			US 2000-207000P	P	20000524
			US 2000-225045P	P	20000811
			US 2001-863804	A1	20010524
			US 2001-863819	A3	20010524
			US 2001-863905	A1	20010524
			WO 2001-US16757	W	20010524
			US 2002-243663	B1	20020916
			US 2002-243942	A1	20020916

OTHER SOURCE(S): MARPAT 136:697

AB The present invention is directed to Mannich base prodrugs of certain 3-(pyrrol-2-ylmethylidene)-2-indolinone derivs. that modulate the activity of protein kinases ("PKs"). **Pharmaceutical compns.** comprising these compds., methods of **treating diseases** related to abnormal PK activity utilizing **pharmaceutical compns.** comprising these compds. and methods of preparing them are also disclosed.

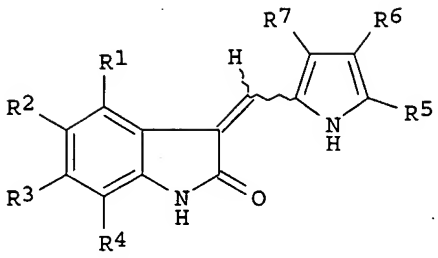
L73 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:617993 CAPLUS
DOCUMENT NUMBER: 135:195497
TITLE: Preparation of pyrrole substituted 2-indolinone protein kinase inhibitors for treatment of cancer
INVENTOR(S): **Tang, Peng Cho**; Miller, Todd; Li, Xiaoyuan; **Sun, Li**; Wei, Chung Chen; Shirazian, Shahrzad; Liang, Congxin; Vojkovsky, Tomas; Nematalla, Asaad S.
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 225 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

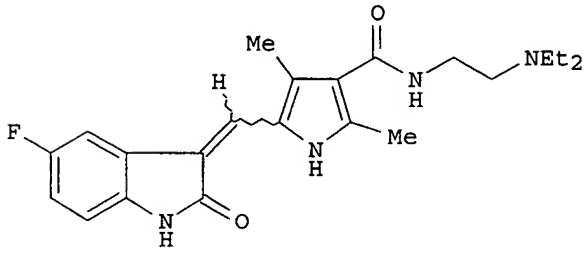
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001060814	A2	20010823	WO 2001-US4813		20010215
WO 2001060814	A3	20020124			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2399358	AA	20010823	CA 2001-2399358		20010215
US 2002156292	A1	20021024	US 2001-783264		20010215
US 6573293	B2	20030603			
EP 1255752	A2	20021113	EP 2001-914376		20010215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003523340	T2	20030805	JP 2001-560198		20010215
JP 3663382	B2	20050622			
BR 2001008394	A	20040622	BR 2001-8394		20010215
NZ 520640	A	20050429	NZ 2001-520640		20010215
NO 2002003831	A	20021015	NO 2002-3831		20020813
ZA 2002006469	A	20031113	ZA 2002-6469		20020813
BG 107078	A	20030430	BG 2002-107078		20020910
US 2004063773	A1	20040401	US 2003-412690		20030414
US 2005176802	A1	20050811	US 2005-28477		20050104
PRIORITY APPLN. INFO.:			US 2000-182710P	P	20000215
			US 2000-216422P	P	20000706
			US 2000-243532P	P	20001027
			US 2001-783264	A3	20010215
			WO 2001-AU4813	W	20010215
			WO 2001-US4813	W	20010215
			US 2003-412690	A1	20030414
OTHER SOURCE(S):	MARPAT 135:195497				

GI



I



II

AB The title compds. (I) [wherein R1 = H, halo, (cyclo)alkyl, (hetero)aryl, heteroalicyclic, OH, alkoxy, acyl, (un)substituted amino or carbamoyl, etc.; R2 = H, halo, alkyl, trihalomethyl, OH, alkoxy, CN, (hetero)aryl, (un)substituted amino, acyl(amino), or sulfamoyl, etc.; R3 = H, halo, alkyl, trihalomethyl, OH, alkoxy, (hetero)aryl, (un)substituted acyl, (acyl)amino, sulfamoyl, or alkylsulfonyl, etc.; R4 = H, halo, alkyl, OH, alkoxy, or (un)substituted amino; R5 and R6 = independently H, alkyl, or acyl; R7 = H, alkyl, (hetero)aryl, or acyl; and their **pharmaceutically** acceptable salts] were prepared as protein kinase modulators for the treatment of cellular disorders such as cancer. For example, 5-fluoro-1,3-dihydroindol-2-one was condensed with 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide to give II (55%). II exhibited comparable activity against Flk-1 and PDGFRβ and inhibited PDGF-dependent receptor phosphorylation in cells with an IC50 value of approx. 0.03 μM. In efficacy expts. against various cancers in mice, II was well tolerated at 80 mg/kg/day, even when dosed continuously for more than 100 days.

L73 ANSWER 9 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:143055 BIOSIS
DOCUMENT NUMBER: PREV200200143055
TITLE: TSU-68 (SU6668), an anti-angiogenic agent, shows stronger anti-tumor effects against higher VEGF productive and more hypervascular tumors, which are poor prognostic factors in breast cancers.
AUTHOR(S): Chikahisa, L. [Reprint author]; Yonekura, K.; Basaki, Y.; Fujita, H.; Hashimoto, A.; Cherrington, J.; **Shawver, L. K.**; Yamada, Y.; Kitazato, K.
CORPORATE SOURCE: Cancer Research Laboratory, Taiho Pharmaceutical Co., Ltd., Hanno, Saitama, Japan
SOURCE: Breast Cancer Research and Treatment, (October, 2001) Vol. 69, No. 3, pp. 283. print.
Meeting Info.: 24th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, USA. December 10-13, 2001.

CODEN: BCTRD6. ISSN: 0167-6806.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002

L73 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:628660 CAPLUS
DOCUMENT NUMBER: 137:346843
TITLE: Effects of vascular endothelial and platelet-derived growth factor receptor inhibitors on long-term cultures from normal human bone marrow
AUTHOR(S): Duhrsen, Ulrich; Martinez, Tanja; Vohwinkel, Gabi; Ergun, Suleyman; **Sun, Li**; **McMahon, Gerald**; Durig, Jan; Hossfeld, Dieter Kurt; Fiedler, Walter
CORPORATE SOURCE: Zentrum fur Innere Medizin, Abteilung fur Hamatologie, Universitatsklinikum Essen, Germany
SOURCE: Growth Factors (2001), 19(1), 1-17
CODEN: GRFAEC; ISSN: 0897-7194
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endothelial cells and fibroblasts are important constituents of the hemopoietic microenvironment. Growth and function of these cells are controlled by a variety of cytokines, including VEGF and PDGF. The authors analyzed the effects of novel tyrosine kinase inhibitors targeting the VEGF and PDGF receptors (compds. SU5614 and SU5768) on the performance of long-term cultures from normal human bone marrow. In developing cultures, the inhibitors induced a dose-dependent reduction in stromal fibroblasts, macrophages and endothelial cells with a concomitant decrease in blood cell production and an increase in fat cells. For SU5614, the concentration inhibiting stroma formation by 50% (IC50) was 123 nM, and the IC50 for hemopoietic colony forming cell output was 186 nM. For SU5768, the resp. values were 871 nM and 331 nM. Changes in stroma **composition** and inhibition of hemopoietic cell production were also demonstrable after delayed addition of the inhibitors to established cultures. By contrast, hemopoietic colony formation in clonogenic agar cultures was unimpaired (IC50 not reached at 100 μM). Immunofluorescence studies and time course analyses suggested that the primary effect of the inhibitors was interference with the proliferation and function of fibroblasts and endothelial cells which in turn resulted in decreased hemopoiesis and increased adipogenesis. This was associated with decreased levels in conditioned media of granulocyte-macrophage colony-stimulating factor, interleukin-6 and leptin. VEGF and PDGF may play a hitherto underestimated role in the control of blood cell formation. VEGF/PDGF receptor inhibitors may have **therapeutic** potential in stroma **diseases** such as myelofibrosis. Since they weaken the stimulatory signals provided by the microenvironment, they may also be of value in the treatment of leukemia and other neoplastic bone marrow diseases.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L73 ANSWER 11 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:301449 BIOSIS
DOCUMENT NUMBER: PREV200100301449

TITLE: Effects of vascular endothelial and platelet-derived growth factor receptor inhibitors on long-term cultures from normal human bone marrow.
AUTHOR(S): Duehrsen, U. [Reprint author]; **Sun, Li**; **McMahon, G.**; Duerig, J. [Reprint author]; Fiedler, W.
CORPORATE SOURCE: University Hospital, Essen, Germany
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 308a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jun 2001
Last Updated on STN: 19 Feb 2002

AB Bone marrow endothelial cells and fibroblasts are critically involved in the regulation of blood cell production. Growth and function of endothelial cells and fibroblasts are controlled by a variety of cytokines, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). We analyzed the effects of novel tyrosine kinase inhibitors targeting the VEGF and PDGF receptors (compounds SU5614 and SU5768) on the performance of human long-term marrow cultures. In developing cultures, the inhibitors induced a dose-dependent reduction in the numbers of stromal fibroblasts, macrophages and endothelial cells with a concomitant decrease in blood cell production and an increase in fat cells. For SU5614, the concentration inhibiting stroma formation by 50 % (IC50) was 123 nM, and the IC50 for hemopoietic colony forming cell output was 186 nM. For SU5768, the respective values were 871 nM and 331 nM. Changes in stroma **composition** and inhibition of hemopoietic cell production were also demonstrable after delayed addition of the inhibitors to established cultures. By contrast, hemopoietic colony formation in agar cultures was unimpaired (IC50 not reached at 100 muM). Immunofluorescence studies and time course analyses suggested that the primary effect of the inhibitors was interference with the proliferation and function of fibroblasts and endothelial cells which in turn resulted in decreased hemopoiesis and increased adipogenesis. This was associated with decreased levels in conditioned media of various hemopoiesis-stimulating cytokines. Thus, VEGF and PDGF may play a hitherto underestimated role in the control of blood cell formation. VEGF/PDGF receptor inhibitors may have **therapeutic** potential in stroma **diseases** such as myelofibrosis. Since the inhibitors weaken the hemopoiesis-stimulating signals provided by the microenvironment, they may also be of value in the treatment of leukemia and other neoplastic bone marrow diseases.

L73 ANSWER 12 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:21857 BIOSIS
DOCUMENT NUMBER: PREV200000021857
TITLE: First preclinical and clinical results with the antiangiogenetic substance SU 5416 in malignancies.
AUTHOR(S): Scigalla, Paul [Reprint author]; Hannah, Alison [Reprint author]; Langecker, Peter [Reprint author]; **Shawver, Laura** [Reprint author]; McMahon, Jeromy [Reprint author]; Hirth, Peter [Reprint author]
CORPORATE SOURCE: SUGEN Inc., San Francisco, CA, USA

SOURCE: European Journal of Cancer, (Oct., 1999) Vol. 35, No. SUPPL. 5, pp. S62. print.
Meeting Info.: 5th International Symposium on the Biological Therapy of Cancer: From Basic Research to Clinical Applications. Munich, Germany. October 27-30, 1999. Biological Therapeutics Development Group of the European Organisation for Research and Treatment of Cancer.
CODEN: EJCAEL. ISSN: 0959-8049.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Dec 1999
Last Updated on STN: 31 Dec 2001

L73 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:640690 CAPLUS
DOCUMENT NUMBER: 127:314804
TITLE: Assays for KDR/FLK-1 receptor tyrosine kinase inhibitors, and use of the inhibitors for **treatment** of vasculogenesis- and angiogenesis-related **diseases**
INVENTOR(S): Hirth, Klaus P.; **McMahon, Gerald**; **Shawver, Laura K.**
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9734920	A1	19970925	WO 1997-US3378	19970304
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9720667	A1	19971010	AU 1997-20667	19970304
PRIORITY APPLN. INFO.:			US 1996-621734 A	19960321
			WO 1997-US3378 W	19970304

AB Processes are disclosed for the identification of compds. and **pharmaceutical compns.** capable of selectively and potently inhibiting KDR/FLK-1 tyrosine kinase signal transduction in order to inhibit vasculogenesis and/or angiogenesis. The invention also relates to compds. and **compns.** identified using the methods of the invention and the use thereof for the **treatment** of **disease** relating to inappropriate vasculogenesis and/or angiogenesis. The invention provides an assay cascade comprised of several "filter steps" of increasing selectivity which identify a limited subset of candidate compds. affecting the VEGF receptor on the mol. level.

=> dis his

(FILE 'HOME' ENTERED AT 14:56:18 ON 19 AUG 2005)

```
     FILE 'REGISTRY' ENTERED AT 14:58:18 ON 19 AUG 2005
L1                STR
L2              0 S L1
L3              1 S L1 FUL

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:00:16 ON 19 AUG 2005
L4              0 FILE MEDLINE
L5              0 FILE BIOSIS
L6              0 FILE EMBASE
L7              1 FILE CAPLUS
     TOTAL FOR ALL FILES
L8              1 S L3

     FILE 'REGISTRY' ENTERED AT 15:01:53 ON 19 AUG 2005
L9                STR L1
L10            50 S L9
L11          5788 S L9 FUL

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:04:10 ON 19 AUG 2005
L12            36 FILE MEDLINE
L13           337 FILE BIOSIS
L14           964 FILE EMBASE
L15           522 FILE CAPLUS
     TOTAL FOR ALL FILES
L16          1859 S L11
L17       2428283 FILE MEDLINE
L18       3250801 FILE BIOSIS
L19       1419137 FILE EMBASE
L20       3099346 FILE CAPLUS
     TOTAL FOR ALL FILES
L21      10197567 S (PHARMAC? OR COMBINATOR? LIBRAR? OR COMPOS?)
L22            28 FILE MEDLINE
L23           236 FILE BIOSIS
L24           804 FILE EMBASE
L25           157 FILE CAPLUS
     TOTAL FOR ALL FILES
L26          1225 S L16 AND L21
L27        186701 FILE MEDLINE
L28        365178 FILE BIOSIS
L29        145295 FILE EMBASE
L30        147528 FILE CAPLUS
     TOTAL FOR ALL FILES
L31        844702 S (TREAT? OR PREVENT? OR THERAP?)(5A)DISEASE?
L32             1 FILE MEDLINE
L33            81 FILE BIOSIS
L34            85 FILE EMBASE
L35            43 FILE CAPLUS
     TOTAL FOR ALL FILES
L36           210 S L26 AND L31
L37           447 FILE MEDLINE
L38           676 FILE BIOSIS
L39           302 FILE EMBASE
L40           943 FILE CAPLUS
     TOTAL FOR ALL FILES
L41          2368 S TANG P?/AU
L42          1354 FILE MEDLINE
L43          1773 FILE BIOSIS
L44          1108 FILE EMBASE
L45          4875 FILE CAPLUS
     TOTAL FOR ALL FILES
```

```
L46          9110 S SUN L?/AU
L47           122 FILE MEDLINE
L48           223 FILE BIOSIS
L49           106 FILE EMBASE
L50           220 FILE CAPLUS
     TOTAL FOR ALL FILES
L51           671 S MCMAHON G?/AU
L52            53 FILE MEDLINE
L53            99 FILE BIOSIS
L54            54 FILE EMBASE
L55            65 FILE CAPLUS
     TOTAL FOR ALL FILES
L56           271 S SHAWVER L?/AU
L57             0 FILE MEDLINE
L58             2 FILE BIOSIS
L59             0 FILE EMBASE
L60             3 FILE CAPLUS
     TOTAL FOR ALL FILES
L61             5 S L41 AND L46 AND L51 AND L56
L62             5 DUP REM L61 (0 DUPLICATES REMOVED)
L63             0 FILE MEDLINE
L64             5 FILE BIOSIS
L65             0 FILE EMBASE
L66            10 FILE CAPLUS
     TOTAL FOR ALL FILES
L67            15 S L36 AND (L41 OR L46 OR L51 OR L56)
L68             0 FILE MEDLINE
L69             5 FILE BIOSIS
L70             0 FILE EMBASE
L71             8 FILE CAPLUS
     TOTAL FOR ALL FILES
L72            13 S L67 NOT L61
L73            13 DUP REM L72 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 15:09:50 ON 19 AUG 2005

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:10:27 ON 19 AUG 2005

     FILE 'REGISTRY' ENTERED AT 15:11:00 ON 19 AUG 2005

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:12:46 ON 19 AUG 2005

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    46.05     801.13

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -8.03     -13.87

STN INTERNATIONAL LOGOFF AT 15:13:25 ON 19 AUG 2005
```